

Revisions made according to the suggestions of the Reviewers:

- A)** In response to Reviewer #1 we checked and corrected: 1) the numbers of the Figures quoted in the text, 2) arrows in Figure 3B, 3) explained what does 'PL' mean in the Figure 11 legend. In response to comment #4) "I would greatly appreciate discussions regarding the correlation between *H. pylori* infection or carcinogenesis and the data of the authors." we have introduced more **information (highlighted yellow)** into the revised manuscript regarding the correlation between *H. pylori* infection and mucosal defense in aging.
- B)** In response to Reviewer #2 we corrected all minor errors as requested. We agree with the reviewer that the real mechanism of aging still needs further evidence and research. We addressed this by adding into revised Discussion section pertinent **text (highlighted yellow)** under new heading: *Molecular abnormalities in aging – Future directions.*

Response to comments of last reviewer:

We thank the reviewer for reviewing our paper and for the comments. We always welcome and like frank and fair scientific discussion. We were invited by Dr. L.S. Ma, President and Editor-in-Chief of World series to write this **Frontier article**. As we understand these articles are designed as review articles written by leading experts in the field. Therefore, by design it is a review article and as such does not contain new research data but rather a brief summary of the current status. Similarly, some journal, e.g. Gastroenterology (impact factor 12.6) or J. Mol. Med. invite top experts in the field to write review papers and encourage authors to use previously generated data and illustration. This was the case for our paper in Gastroenterology 2007 written by Prof. L. Laine (last year American Gastroenterological Association President), Prof. K. Takeuchi and myself. This was also the case with other invited review by Gastroenterology (ref 35) and also when J. Mol. Med. invited me to write a review article and include data from our previously published paper in Nature Medicine.

We made all efforts to respond positively to this reviewer.

In response to this reviewer's comment regarding introduction we re-arranged the text describing first the gastric mucosal defense, next we described all available work of other authors pertaining to aging gastric mucosa and after that we presented our data reproducing with permission our own illustration. The changes are highlighted in light blue.

Reviewer: Fig 1 was not a scientific data?

Response: **We did not label this picture as Figure 1, it was most likely done by the Editorial Office of WJG. We leave this decision up to the Editorial Office of WJG.**

Reviewer: Fig 3 Please point the oxyntic and parietal cells –since the text explained “degenerative changes in parietal and chief cells..... What is F ? What did arrow indicate?

Response: The figure and the legend were corrected in response to two previous reviewers. In response to this reviewer we eliminated from the text reference to parietal and chief cells and focused on the main finding - disorganized collagen fibrils in connective tissue immediately adjacent to capillary blood vessels, which can interfere with nutrient and oxygen transport and hence lead to hypoxia as well as the accumulation of toxic metabolites. F and arrows are now explained in the revised figure legend.

Reviewer: The citation of reference cited [2] was incorrect.

Response: It would be helpful if the reviewer would provide page and line number for this cited reference. We checked this references and in our opinion it is correct

Reviewer: Fig 4&5 should be alternated – structure shown before function

Response: Figure 4 (previous version of the manuscript) pertained to gastric mucosal defense. It is a schematic representation of gastric mucosal defense mechanisms. Figure 5 pertains to structural components of gastric mucosal defense: surface epithelial cells (SEC), progenitor cells and blood microvessels. They are 2 entirely different series of illustrations.

Reviewer: The citation of references [4] [8] were not correct.

Response: It would be helpful if the reviewer would provide page and line number for these cited references. We checked these references and in our opinion they are correct. Reference [8] is in the text of figure legend for new version of Figure 3.

Reviewer: Fig 7 did not has citation and prove of patent permission

Response: reviewer is possibly referring to “the copyright permission”. Figure 7 had and has in figure legend clearly spelled out “Reproduced with permission from Tarnawski *et al*”.

Reviewer: Fig 8 (A) Real time PCR should be measured or interpreted in fold increased. What the % related to? (B) there was no result of PTEN mRNA

Response: QPCR amplification of GAPDH was carried out in parallel to normalize the input cDNA for each PCR. The graph shows relative PTEN values as a % of GAPDH expression in the sample being assayed. In the figure legend we have added “respectively” to clarify the sentence meaning. It now reads “(A) Real time PCR and (B) Representative Western blots showing a significant increase in PTEN mRNA and protein expression, respectively, in gastric mucosa of aging vs. young rats.”

Reviewer: Fig 9 positive stain increased was more than 6 fold. It should be approximately 8 folds. The last sentence of this fig should be placed in the text at 4)

Response: We re-assessed the staining and agree with the reviewer. The text has been change to reflect a significant increase.

Reviewer: Also describing in the text at 5) - (Fig 9) should be (Fig 10)

Response: We carefully reviewed and corrected Figure numbering.

Reviewer: Fig 11 did not has citation and prove of patent permission

Response: Reviewer is possibly referring to "the copyright permission". Figure 11 had and has in figure legend clearly spelled out "Reproduced with permission from Tarnawski *et al*^[1]".

Mistaken in the text

Reviewer: Cited references [30] [31] [32] [33] [34] did not fitted with the sentences that claimed the results from "we"

Response: "we" refers to the fact that we examined these parameters, while references [30-34] provide information pertaining to Hypoxy-1 probe [30] and PTEN [31-34]. We have revised the text to clarify the sentence meaning.

Reviewer: Cited references described in TUNEL ASSAY [1] [35] were not match. Fig 8 apoptosis was increased

Response: Reference [1] refers to our original study in Gastroenterology 2007, in which we described in more detail TUNEL ASSAY method (and provided relevant references); Reference [35] pertains to the apoptosis-inducing executioner proteases: caspase-3 and caspase-9 described in our previous review paper - invited by Gastroenterology. In response to this reviewer we have revised the text to clarify the sentence meaning.

Reviewer: Discussion on p. 12- the last sentence needs correction, p. 13 -also needs correction

Response: We have moved the text, which was the next heading close to the next sentence.

Reviewer comments

Comments of WJG review article ID 0058340 by Tarnawski AS et al

The review was a summary of Tarnawski's research about the aging mucosa and its increased susceptibility to injury. The authors emphasized on the mechanism of injury and pointed out that since the number of aging population is continue increasing, more attention is required to reduce the risk, the complication and to find the drug against gastric mucosa injury.

Introduction - mostly presented by figures and figure legends which 10 from 11 figures (Fig 2, 3, 4, 5, 6, 8, 9, 10, 11, 12) were copied from the previous works of Tarnawski & Ahluwalia. The text contains quite a small volume of new knowledge besides those already described in their previous publications. (The percent contribution of the work and writing should be given.)

Figures were redundancy and included several mistakes:

Fig 1 was not a scientific data? Please reassure whether it should be presented here.

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The citation of reference cited [2] was incorrect.

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3. Discussion on p. 12- the last sentence needs correction
p. 13 -also needs correction

Thank you for your consideration.

Sincerely yours,

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